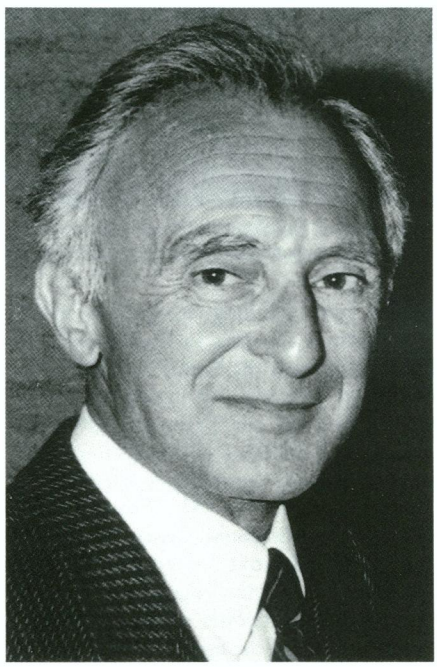
Spheres of Influence

A Distinguished Career in the Service of Cancer Prevention

After devoting more than 26 years to the International Agency for Research on Cancer, the last 12 years as director, Lorenzo Tomatis retired in December 1993. Throughout these years Tomatis has been the tireless embodiment of the IARC's mission: to conduct and coordinate research at an international level aimed at cancer prevention through the application of scientific knowledge of the causes of cancer.

IARC, located in Lyon, France, is an independently financed, intergovernmental organization within the framework of the World Health Organization. Research at IARC, which Tomatis conducted, guided and expanded during his tenure there, is largely multidisciplinary, bringing together the results of epidemiological and laboratory studies and linked by collaborative research agreements with researchers in 56 countries on all 5 continents.


IARC

Early Years

Tomatis was born and had his early education in Italy. He obtained his medical degree from the University of Turin in 1953. After a brief stint as a medical officer with a regiment of Alpine troops, he returned to the university to specialize in occupational diseases. It was here that his interest in the role of chemicals as potential causes of cancer began.

In the mid-1950s, Tomatis was beginning to broaden his horizons and, like other young Italian medical doctors at that time, he saw exciting research opportunities in the United States. In 1959, Tomatis traveled across the Atlantic to join Phillipe Shubik's team at the Division of Oncology in the Chicago Medical School. Shubik's group had already established an international reputation in the field of chemical carcinogenesis, and Tomatis was rapidly absorbed into the team. According to Shubik, now director of the Toxicology Forum in Oxford, even then Tomatis showed great promise as a basic research worker: "He was a careful and thoughtful investigator who was able to think of probable advances before many others. He organized a tissue culture laboratory in my department before this field had achieved its present importance."

Tomatis's enthusiasm and willingness to face a challenge carried over into his personal life as well. Shubik recalls an instance early on in which Tomatis and his wife were visiting with Shubik at his lake house in Canada, having driven from Chicago in an old Chevrolet. Says Shubik, "[The car] had mechanical problems after arrival and the local mechanic wondered if it was adequate to get them home. However, a while later I heard that they had driven it to the Yukon and were continuing to explore North America."

Tomatis's first two publications from Chicago—one on the induction of tumors in the hamster with *o*-amino-azotoluene and the other a study of the role of croton oil in skin carcinogenesis—foretold the scientific path that he has developed and advanced ever since. Interestingly, his coauthors with Shubik were both fellow Italians—Giuseppe Della Porta, on the first paper, former director of the Division of Experimental Oncology in the National Cancer Institute in Milan, and on the second paper, Benedetto Terracini, now chair of the Department of Biomedical Sciences and Human Oncology at the University of Turin.

Tomatis continued to publish throughout his stay in Chicago, but in 1965 his research took an important new direction with a paper in which he reported an increased incidence of tumors in the first (F_1) and second (F_2) generations of offspring from pregnant mice that had been exposed to a polycyclic hydrocarbon, dimethylbenzanthracene. He continued to pioneer this new aspect of carcinogenesis research and was awarded an Eleanor Roosevelt International Cancer Fellowship in 1965–1966 to study the response to neonatal exposure to carcinogens. When he joined IARC following that fellowship, transplacental carcinogenesis was one of the themes that Tomatis pursued with his new colleagues.

Joining IARC

Tomatis joined IARC in November 1967 at the age of 38. He arrived to create and establish the unit of chemical carcinogenesis and spent his career there developing the field in which he had already established his reputation. Studies of perinatal, transplacental, and multigenerational carcinogenesis remained a major interest for Tomatis, and he was quick to see that the emerging field of molecular biology would contribute to a much more refined understanding of the mechanisms that might be involved in the transmission of carcinogenic risk from one generation to another. Says Takashi Sugimura, director of the National Cancer Center in Japan, who is both a friend and colleague of Tomatis, "His pioneering scientific contributions on transplacental carcinogenesis are beginning to focus the attention of more and more scientists on this area of carcinogenesis."

Nikolai P. Napalkov, assistant director-general of the World Health Organization, calls Tomatis's multigenerational studies some of his greatest contributions to the field of carcinogenesis. Napalkov and Tomatis met in the early 1960s when Tomatis was at the Chicago Medical School and Napalkov was also doing research on chemical carcinogenesis at the Sloan Kettering Institute at the University of California at Berkeley. The two became friends and collaborators over the years, working on joint projects in experimental carcinogenesis. Regarding Tomatis's research methods, Napalkov has the highest respect: "Dr. Tomatis has a systematic knowledge of experimental pathology—both human and animal—that is indispensable to [his research] and ensures that his data are always very solid. There is no reason to hesitate about the validity of his findings."

The overall objective of IARC is to prevent human cancer, and identifying environmental carcinogens as the prerequisite for their removal or, at least, reduction, is a major step toward that goal. One of Tomatis's major contributions to IARC

and to global public health was to establish the evidence of animal carcinogenicity in long-term experiments as a valid criterion for evaluating possible carcinogenic risks to humans, alongside or, even more importantly, in the absence of, epidemiological evidence. Tomatis worked to establish this balanced perspective in which human epidemiology and experimental results are both seen as essential to the identification of human risks.

Tomatis also forecast the advantage of developing short-term *in vitro* mutagenicity assays, which could serve as valuable indicators of substances that needed further study. In addition, Tomatis encouraged research on the role of host factors, such as endogenous activation of xenobiotic chemicals, in carcinogenesis and into the mechanisms of action of carcinogens, concentrating particularly on the interaction between carcinogens and DNA—research that IARC intends not only continue, but to expand in the coming years.

A Crowning Achievement

In 1969, Tomatis initiated what has become in the eyes of many IARC's singular most important contribution to cancer prevention, its Programme on the Evaluation of Carcinogenic Risks to Humans and the publication of the program's findings in a monograph series. The program has won an international reputation for its scientific validity, impartiality, and integrity and for its contribution to preventive measures and public health. Says Sugimura of the monograph series, "I can say that many regulatory, academic, and industrial communities draw practically their entire evaluation of chemical risk from them."

The first working group of internationally recognized experts, chaired by Shubik, met in Lyon in December 1970 to prepare the scientific criteria that would be used in the monographs of the program and to make preliminary evaluations of the data on five substances. These 5 evaluations, together with those of 14 more substances, were considered by a working group that met in December 1971, and made up the first volume of the IARC Monograph Series which was published in 1972, covering organic, inorganic, and natural products. The initial volume was well received and the program was truly launched. Since then, with the scientific collaboration and financial support of the U.S. National Cancer Institute, NIEHS, and the Commission of the European Communities, among others, the program has undergone considerable expansion.

To date, 58 volumes of monographs (often referred to as "orange books" because of the color of their covers) have been published, and another is currently in press. Every effort has been made to ensure the maximum dissemination of these evaluations both to national health authorities and the scientific community. The monographs, which began with evaluations on man-made and naturally occurring chemicals, have greatly widened in scope in the more than 20 years of their existence to include evaluations of myriad exposure circumstances such as industrial processes and occupations and lifestyle risk factors such as diet, drugs, alcohol, and cigarette smoking. It is perhaps for his continuous efforts in publishing the monograph series that Tomatis is most highly regarded. David P. Rall, former director of NIEHS and a colleague of Tomatis's for more than 20 years says, "To keep the series running for 20 years and to maintain it at such a high level is an unprecedented achievement." According to Sugimura, the monographs represent a continuing legacy from Tomatis that can never be forgotten; Sugimura calls the monographs "a box of jewels of the knowledge of mankind on chemical carcinogenesis."

Parallel to the development of the monographs program, IARC has made an effort to rationalize carcinogenicity testing at the international level. Because animal experiments are costly and take several years to complete, it is important to know who is testing what before setting up a series of experiments in order to avoid unnecessary duplication of work and build on the research of others. To facilitate this kind of communication, IARC has published Information Bulletins periodically since 1973, now called the *Directory of Agents Being Tested for Carcinogenicity*. These directories provide companion and cross-linked volumes to the annual *Directories of On-going Research in Cancer Epidemiology*, also published by IARC.

Global Vision

When Tomatis assumed the responsibilities of director of IARC in 1982, not only did he work to further apply and integrate his well-established philosophy of developing the interaction between experimental research and epidemiology studies, but he expanded his efforts to strengthen the role of IARC, not just in identifying cancer risks, but in research into different aspects of cancer prevention and control. An outstanding example is the Gambia Hepatitis Intervention Study, where a plan for countrywide hepatitis vaccination of all newborn children has been set up, in conjunction with a cancer registration scheme, that will produce important information on the effectiveness of this measure in preventing primary liver cancer.

Apart from the important and fundamental scientific aspects of the Gambia study, it is not incidental that Tomatis should give support to a study in a developing country; many of his writings have demonstrated his consciousness of the social aspects of the cancer problem throughout the world. It is evident that Tomatis views cancer not just as multiple diseases, but more as a global public health problem. In that context, he has drawn attention to the relationship between poverty and cancer risk, not only in developing countries but also in industrialized countries where higher cancer risks and lower socioeconomic class go hand in hand. This perspective is spelled out in detail in an editorial Tomatis wrote last year on poverty and cancer published in *Cancer Epidemiology, Biomarkers and Prevention*. Other examples of this commitment to extending IARC's research activities abound and include study of the risks of occupational exposures in newly industrialized societies and assessment of the effects that the spread of the AIDS virus might have on the burden of cancer.

In 1990, IARC published *Cancer: Causes, Occurrence and Control*, a synthesis of current scientific knowledge and philosophy relating to cancer causation and prevention that attempts to quantify on a global scale the benefits of the practical application of this knowledge. Tomatis was both inspirer and editor-in-chief of this book, to which most of the IARC scientists contributed. At the end of the introduction to this book, Tomatis sets out his thoughts on cancer policy and priorities, of which two points stand out as what he believes are limiting factors in the successful development of research in cancer prevention. One, says Tomatis, is "the competition between military expenditures . . . and funds allocated for education and health." The other is the consideration of basic and applied research as separate and competing areas, which he calls "a grave error, which can only serve the purpose of preventing scientists from forming a common front in spending the available resources rationally and efficiently and perhaps obtaining more of them."

A Man of Many Talents

Although Tomatis's more than 200 scientific publications are available and accessible to all those who can read English, hidden from all except those who read Italian are the literary works signed by Renzo Tomatis.

His first book, *Il Laboratorio* (*The Laboratory*), was published in 1965 and is based on his own daybook during one year (1962–63) in Shubik's laboratory in Chicago. The book, which reveals an accomplished literary style, may be read as

a presentation for the layman of the daily work of a young scientist, as well as a comparison of the Italian and the American ways of life. *Il Laboratorio* earned popularity in Italy, particularly among young researchers, mainly for its lucid and open critique of the scientific establishment of their country, in particular of the archaic structure of the university. As a testament to his writing skills, Napalkov says that Tomatis proved to be so clever in his depictions of Italian academics and scientists that "it was clear soon after the book's publication that he would never be able to pursue his career in Italy." What may have been Italy's loss has certainly been the world's gain.

The extent of Tomatis's influence on the field of cancer prevention is accountable, in large part, to what Sugimura calls his "vast knowledge on chemical carcinogenesis" and his "sincere and noble personality as a scientific leader," which has enabled him to guide and develop one of the leading research agencies in the world. On a more personal level, he is described by his colleagues as having "sharp eyes and a good sense of humor," "a knowledge of all the wonderful restaurants in and around Lyon," and a "good sense of art history, as well as a philosophical approach to many life problems," all of which no doubt have served to enrich not only his own life, but the lives of those with whom he has come into contact.

Tomatis's other literary works, *La Ricerca Illimitata* (*The Unlimited Research*, 1974), *Visto dall'Interno* (*Seen from the Inside*, 1981), and *Storia Naturale di un Ricercatore* (*Natural History of a Researcher*, 1985), have all had considerable, if somewhat lesser, impact on the Italian scientific community. In these books Tomatis explores the theme of the social implications of science—and of medical research in particular—as he continuously poses the question of what is the ultimate goal of the work of the scientist, split between personal ambition and the general good. The reader finds perhaps more questions than answers in his books; the answers have to be sought in the life of Lorenzo Tomatis—a life which continues to be conducted with scientific rigor and moral integrity.

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